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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,253	BRINKMANN ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/7/06; 8/22/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *1-18,20-28,30,31,36,37 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,29,32-35 and 38-41* is/are rejected.

7)☒ Claim(s) *29,34 and 38-41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group VII, further electing SEQ ID NO: 171 in the reply filed on 8/22/06, affirmed in the paper filed 12/7/06, is acknowledged. Applicant traverses the restriction among groups I-IX stating that they believe that many of these groups could be searched and prosecuted in this application without undue burden. This is not persuasive. First, the separate classification of the groups is evidence of search burden. Further, the searches for the groups are not coextensive. For example, a search of the elected methods for detecting a particular SNP and diseases would not identify references concerning transgenic non-human animals. Applicant further traverses the restriction among different nucleic acid sequences because the division into thousand of individual subject matters for separate prosecution is unduly burdensome and economically unfeasible for applicants. As stated in the restriction requirement, claims to sequences with unique structure represent distinct inventions, and the search and examination for each of these is not coextensive and would be unduly burdensome for the examiner. Applicant has not provided argument against these factors for determining the propriety of restriction. The restriction is maintained and made final.

2. Claims 19, 29, 32, 33, 34, 35, and 38-41 are under prosecution in this office action.

Claim Objections

3. Claim 29 is objected to because of the following informalities: The claim does not end with a period. MPEP 608.01(m) states, "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations."

4. Claim 34 is objected to because of the following informalities: The word polynucleotides is misspelled in line 4 of the claim. There should be a space between the words "polynucleotide" and "with" in line 5 of the claim.

5. Claim 38 is objected to because it ends in two periods.

6. Claim 39 is objected to because it appears there should be an "a" between the words "using" and "polynucleotide" in lines 2-3 of the claims.

7. Claims 40 and 41 are objected to because they are improper dependent claims. The further limitations modify the intended use of the claims but do not appear to further limit the practice of the method.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 29, 32, 33, 34, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29, 32, and 33 are indefinite because the claim sets forth a preamble of "diagnosing a disorder related to the presence of a MRP-1 gene or susceptibility to such a disorder," but the claims set forth only method steps set forth related to "determining the presence of a polynucleotide having the nucleic acid sequence of SEQ ID NO: 171 in a sample from a subject. The claims do not set forth how the determining is related to the diagnosing, and

so it is confusing if applicant intends to be claiming a method for diagnosing disease or susceptibility to disease or if applicant intends simply to be claiming any method for determining the presence of a polynucleotide in a sample.

Claims 34 and 35 are indefinite over the phrase "vectors or host cells characterized by that polynucleotide" because it is not clear if all or part of SEQ ID NO: 171 must be present in order for a construct to be characterized by the sequence. Furthermore, the claims are indefinite because they set forth in the preamble that they are a method of detection of a polynucleotide having the nucleic acid sequence of SEQ ID NO: 171 in a sample, but they do not set forth a method step which requires accomplishing this end. The method step requires determining binding of a polynucleotide to SEQ ID NO: 171, but such binding could occur by molecules that are close in sequence to instant SEQ ID NO: 171 but are not completely identical to instant SEQ ID NO: 171. Therefore, it is not clear if the method is intended to encompass only methods for detecting instant SEQ ID NO: 171 or methods for detecting all molecules that hybridize to instant SEQ ID NO: 171.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 19, 29, 32, 33, 34, 35, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is enabling for methods which detect that a human is homozygous for the presence of instant SEQ ID NO: 171 as an indicator of increased likelihood of having drug induced hepatic toxicity or that detect in a human the presence of instant SEQ ID NO: 171 as an indicator of a decrease in expression of the gene which comprises instant SEQ ID NO: 171 relative to individuals who do not have instant SEQ ID NO: 171. The specification is also enabling for preparing compositions for determining such increased likelihood of drug induced hepatic toxicity. The specification is not enabling for the detection of polymorphisms in any or all species of individuals, the specification is not enabling for methods which diagnose any disease or phenotype, any cancer, etc, the specification is not enabling for methods which recite a relationship between instant SEQ ID NO: 171 and the presence of cancer, the specification is not enabling detecting polymorphisms in individuals with any or all "MDR-1 related diseases," the specification is not enabling for preparing compositions for diagnosing any disease, nor is the specification enabling for preparing any pharmaceutical composition comprising instant SEQ ID NO: 171.

Nature of the Invention

The invention is drawn to methods which utilize or prepare instant SEQ ID NO: 171. Instant SEQ ID NO: 171 is a nucleic acid molecule that overlaps with a polymorphic position in the human multidrug resistance protein-1. The polymorphism is referred to in the specification as an exon 9 T95C polymorphism referring to the fact that the polymorphism is in exon 9 of the gene at the 95th position of the exon. Instant SEQ ID NO: 171 has the "C" allele present. The

claims include claims for identifying polymorphisms, diagnosing a disorder, detecting polynucleotides, and preparing diagnostic and pharmaceutical compositions. The nature of the invention, therefore, requires knowledge of how SEQ ID NO: 171 is associated with particular diseases and for claims 39-41 also how instant SEQ ID NO: 171 might be used as a pharmaceutical for treating a disease.

Scope of the Claims

Each of the rejected claims has at least one aspect of the claim which is very broad. All of the claims are sufficiently broad so as to encompass the analysis, diagnosis, detection, and/or treatment of non-human subjects.

Regarding claim 19, recites subjects that have "MRP-1 associated disease." There is no universally known group of diseases that are "MRP-1 associated."

Regarding claim 29, this claim is sufficiently broad so as to encompass diagnosing any possible disorder related to the presence of SEQ ID NO: 171 in a genetic sample from a subject. Regarding claim 32, the claim is sufficiently broad so as to encompass the diagnosis of any type of cancer. Claim 35 likewise sets forth a method for diagnosing a disease (any possible disease) based upon the binding of a sample nucleic acid to SEQ ID NO: 171. This claim does not even require that the mutant "C" allele is present in the sample, as under some hybridization conditions either allele would be expected to hybridize to SEQ ID NO: 171.

Claim 38 is drawn to a method for preparing a diagnostic composition for diagnosing a disease. This claim is rejected for lack of enablement to address the intended use portion of the claim. The claim sets forth "isolating, preparing, or using" a polynucleotide having instant SEQ

ID NO: 171 for the diagnosis of any possible disease, with claims 40 and 41 setting forth that the disease is cancer of a disease related to multidrug resistance, more specifically, renal cancer.

Regarding claim 39, this claim is drawn to preparing a "pharmaceutical composition for treating disease." This claim is rejected for lack of enablement to address the intended use portion of the claim. The claim sets forth "isolating, preparing, or using" a polynucleotide having instant SEQ ID NO: 171 for the treatment of any possible disease, with claims 40 and 41 setting forth that the disease is cancer of a disease related to multidrug resistance, more specifically, renal cancer.

Teachings in the Specification

Example 1 of the specification teaches the isolation of genomic DNA from human blood and the generation of MRP-1 fragments. These fragments were sequenced from 24 individuals and compared (Example 2, p. 41). Forty-two different single nucleotide polymorphisms were identified. Example 4 of the specification provides an analysis of alleles of the newly identified SNP in a group of samples from patients with renal cell carcinoma and healthy controls. The elected SNP is identified on p. 48 of the specification as a T95C (exon 9, Asn to Asn) SNP. The allele frequencies for this SNP were very close in cases and controls. There does not appear to be a statistically significant difference in allele frequency between cases and controls. Example 5 of the specification teaches statistical analysis of correlations between MRP-1 SNP and renal cell carcinoma, teaching that statistical evaluations were performed to test for differences in allele frequencies between patients with RCC and controls. The example provides data for three SNP in the MRP-1 gene, but none for the exon 9 T95C SNP (p. 52). Applicant teaches in example 7 that a correlation of MPR-1 mRNA expression was found with the T95C, exon 9 SNP

(p. 55). Applicant teaches in example 8 that the T95C SNP is associated with drug-induced hepatic toxicity, namely that the frequency of homozygous mutants is elevated in patients having liver toxicity versus healthy controls.

The specification teaches on p. 72 that the T95C SNP is located in exon 9 of the MPR-1 gene, and the table gives the nucleotide context of the SNP as being within instant SEQ ID NO: 171, with SEQ ID NO: 172 being the complement of SEQ ID NO: 171. The "T" allele is given in SEQ ID NO: 167 and 168, and SEQ ID NO: 169 and 170 give the surrounding context with a t/c in the polymorphic position.

Regarding claim 19, the practice of this invention requires being able to identify subgroups of individuals that have a "MRP-1 associated disease." There is no universally known group of diseases that are MRP-1 associated. The specification demonstrates that drug induced hepatic failure is associated with the homozygous "C" allele of the position 95 exon 9 polymorphism, and the specification teaches an association between RCC and some MRP-1 SNP. The specification is silent as to other diseases that are MRP-1 associated diseases.

Regarding claim 29, this claim is sufficiently broad so as to encompass diagnosing any possible disorder related to the presence of SEQ ID NO: 171 in a genetic sample from a subject. Claim 35 likewise sets forth a method for diagnosing a disease (any possible disease) based upon the binding of a sample nucleic acid to SEQ ID NO: 171. This claim does not even require that the mutant "C" allele is present in the sample, as under some hybridization conditions either allele would be expected to hybridize to SEQ ID NO: 171. The specification teaches that the frequency of individuals homozygous for SEQ ID NO: 171 is elevated in patients having liver toxicity versus healthy controls. The specification does not establish that this relationship exists

for any other disorders, nor does the specification teach that the presence of SEQ ID NO: 171 necessarily means that even drug induced liver toxicity is present- as is implied by the preamble of the claim which recites a method for "diagnosis." Regarding claim 32, the specification failed to demonstrate an association between the presence of SEQ ID NO: 171 and any type of cancer.

Claim 38 is drawn to a method for preparing a diagnostic composition for diagnosing a disease. This claim is rejected for lack of enablement to address the intended use portion of the claim. The claim sets forth "isolating, preparing, or using" a polynucleotide having instant SEQ ID NO: 171 for the diagnosis of any possible disease, with claims 40 and 41 setting forth that the disease is cancer of a disease related to multidrug resistance, more specifically, renal cancer. As previously discussed, the specification teaches an association between SEQ ID NO: 171 and only a single disease or disorder, namely, drug induced hepatic failure. Regarding claim 39, this claim is drawn to preparing a "pharmaceutical composition for treating disease." This claim is rejected for lack of enablement to address the intended use portion of the claim. The claim sets forth "isolating, preparing, or using" a polynucleotide having instant SEQ ID NO: 171 for the treatment of any possible disease, with claims 40 and 41 setting forth that the disease is cancer of a disease related to multidrug resistance, more specifically, renal cancer. The specification does not provide any examples which use SEQ ID NO: 171 in the TREATMENT of any disease.

State of the Prior Art

At the time the invention was made, the human multidrug related protein-1 gene was known, as was a the disclosed polymorphism. Zaman et al. teach the cloning and sequencing of the MRP cDNA, and teach a silent variation referred to as T-1258→C which is within the same nucleotide context as the instant polymorphism (PNAS USA 91:8822-8826, September 1994).

Zaman et al. use numbering according to Cole et al., and in the sequence taught by Cole et al. position 1258 overlaps with instant SEQ ID NO: 171 (see GenBank Accession L05628; GI: 292332; March 29, 1993). Furthermore, the polymorphism is disclosed in GenBank X78338 which provides mRNA encoding the human MRP and teaches a variation at position 1199 of that sequence, namely where a "c" is replaced with a "t." The prior art does not provide any data concerning the effect this polymorphism has on the encoded polypeptide or the expression of the gene or any relationship between this polymorphism and any disease. Furthermore, the prior art does not define a class of diseases which are known as "MRP-1" related or associated diseases. The prior art does not provide any guidance as to how instant SEQ ID NO: 171 is to be used as a pharmaceutical.

Level of Unpredictability

The instant specification demonstrates that the association of a polymorphism with any phenotype is highly unpredictable. For example, the specification demonstrates in the examples that all of the identified polymorphisms are not associated with RCC, but some are. The exon 9 T95C polymorphism was not associated with RCC but was associated with gene expression and drug induced renal failure. It is highly unpredictable which other diseases the polymorphism might be associated with.

The prior art teaches the unpredictability of using nucleic acid sequence analysis for the determination of a phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Additionally, post-filing art reveals that most gene

association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Thus, it is highly unpredictable what phenotypes, besides drug induced hepatic failure and gene expression levels the exon 9 C95T polymorphism is associated with.

The technology is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. First, it is the instantly disclosed polymorphism is present in the genomes of other organisms, other than humans. Genetic polymorphisms are the elements which render individuals unique, but many genes are highly conserved and do not yield polymorphisms between individuals of a single species. Some genes even lack polymorphisms between members of the same species. The specification and prior art provide no guidance as to whether any other polymorphisms exist, or whether the instantly disclosed polymorphism is present in the genomes of other animals besides humans. Second, after a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any or all diseases, and more particularly and or all cancers, and even more particularly, RCC. Thus, the claimed methods of diagnosis, for enablement of the full scope, requires the application of the knowledge of unknown and unpredictable associations between particular alleles of the exon 9 polymorphism and phenotypes. In this case, the genus is itself

undefined and undue experimentation is required to identify which polymorphisms, none of which are known other than the disclosed example, have the utility of being associated with favorable meat quality.

Furthermore, it is entirely unpredictable whether or not the MRP-1 genes of any other organisms contain a SNP at a position homologous to that described in the instant specification for the human MRP-1 gene and whether or not such a polymorphism would be indicative of any phenotypic traits, such as gene expression levels and/or drug induced hepatic failure. The unpredictability of the interspecies conservation of polymorphic sites is demonstrated in the prior art of Mummidi et al (2000). Mummidi et al teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that some positions that are polymorphic in the human gene are not polymorphic in other non-primate animals, and vice versa (p.18950, Fig 1).

The converse line of reasoning demonstrates that just finding a identifying a MRP-1 gene in an animal other than a humans does not necessarily mean that a polymorphism in the gene will be predictive any particular phenotype. It is possible that an apparent MRP-1 homolog in a non-human animal might not be functionally equivalent to the MRP-1 gene in humans. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus, even if homologs of the MRP-1 gene were identified and sequenced in other animals, and even if these new MRP-1 genes displayed polymorphisms, one would have to perform a large amount of experimentation to determine

whether or not these putative polymorphisms would be indicative of any particular traits in the animals.

Furthermore, claims 39-41 recite a method for preparing a pharmaceutical composition for treating disease, in particular cancer or a disease related to multidrug resistance, more particularly, renal cancer. It is highly unpredictable how or if instant SEQ ID NO: 1 can be used within a pharmaceutical composition for the treatment of disease.

Quantity of Experimentation

The practice of the claimed invention would require enormous levels of experimentation within a highly unpredictable technology area in order to establish relationships between any and all diseases, cancers in particular, and the exon 9 C95T polymorphisms. One would have to establish a class of diseases which are MPR-1 related diseases and which are diagnosed by or treated with instant SEQ ID NO: 171. The research would require extensive screening to identify the polymorphism within populations and to then establish relationships between the polymorphism and phenotypes. The research required to establish if and how instant SEQ ID NO: 171 can be used for the treatment of disease would require experimentation in animal models and humans to establish whether and how the nucleotide fragment can be used as a pharmaceutical.

Conclusion

Thus, having carefully considered all of these factors, it is concluded that it would require undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 29, 32, 33, 38, 39, 40, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Zaman et al. (PNAS USA 91:8822-8826, September 1994), as evidenced by Cole et al. GenBank L05628, 29 March 1993.

Zaman et al. teach a method comprising determining the presence of a polynucleotide having the nucleic acid sequence of SEQ ID NO: 171 in a sample from a subject. Zaman et al. teach the cloning and sequencing of the MRP cDNA, and teach detecting a silent variation referred to as T-1258→C which is within the same nucleotide context as the instant polymorphism (p. 8823). Zaman et al. use numbering according to Cole et al., and in the sequence taught by Cole et al. position 1258 overlaps with instant SEQ ID NO: 171 (see GenBank Accession L05628; GI: 292332; March 29, 1993). Thus, Zaman et al. teach a method wherein instant SEQ ID NO: 171 is detected. This method anticipates the single method step set forth for claims 29, 32, and 33. Regarding claim 33, Zaman et al. teach determining the presence of the sequence using direct sequencing (p. 8822).

Regarding claims 38-40, Zaman et al. thus teach a method comprising the step of isolating a polynucleotide having the nucleic acid sequence of SEQ ID NO: 171.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zaman et al. (as evidenced by Cole et al.) in view of Rund et al. (Adv Exp Med Biol. 1999;457:71-5).

Zaman et al. teach a method comprising isolating a polynucleotide having the nucleic acid sequence of SEQ ID NO: 171 and identifying a single nucleotide polymorphism by comparing the nucleic acid sequence of said polynucleotide with one or more further polynucleotide from the same gene. Zaman et al. teach the cloning and sequencing of the MRP cDNA, and teach detecting a silent variation referred to as T-1258→C which is within the same nucleotide context as the instant polymorphism (p. 8823). Zaman et al. use numbering according to Cole et al., and in the sequence taught by Cole et al. position 1258 overlaps with instant SEQ ID NO: 171 (see GenBank Accession L05628; GI: 292332; March 29, 1993). Zaman et al. teach that MRP is a overexpressed in different drug resistant cell lines (p. 8822) and that MRP is a plasma membrane drug pump.

Zaman et al. teach that polymorphisms exist with in the human MRP gene, but they do not teach a method in which a plurality of subgroups wherein one subgroup has no prevalence for a MRP-1 associated disease is compared to a subgroup that does not have prevalence for a MRP-1 associated disease.

Rund et al. teaches the detection of polymorphisms the human multidrug resistance gene among subgroups that have leukemia versus control subjects, and they determine the presence of a polymorphism within the MDR gene.

It would have been prima facie obvious to one of ordinary skill in the art to modify the methods taught by Zaman et al. so as to have identified polymorphisms within the human MRP gene by comparing the nucleic acid sequence of molecules comprising instant SEQ ID NO: 171 in patients which have multidrug resistant disease versus those that do not have such disease, as exemplified by Rund et al. One would have been motivated to undertake such experiments because Zaman et al. teach that MRP is related a phenotype similar to that related to MDR expression (that is multidrug resistance) and one would have been motivated to further study the MDR-1 gene in diseased and control patients to elucidate the relationship between gene variants and phenotype.

16. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zaman et al. in view of Cole et al. (Science, vol. 258, December 1992, pages 1650-1654).

Zaman et al. teach a method comprising isolating a polynucleotide having the nucleic acid sequence of SEQ ID NO: 171 and identifying a single nucleotide polymorphism by comparing the nucleic acid sequence of said polynucleotide with one or more further polynucleotide from the same gene. Zaman et al. teach the cloning and sequencing of the MRP cDNA, and teach detecting a silent variation referred to as T-1258→C which is within the same nucleotide context as the instant polymorphism (p. 8823). Zaman et al. use numbering according to Cole et al., and in the sequence taught by Cole et al. position 1258 overlaps with instant SEQ ID NO: 171 (see Cole et al. note numbered 31 and GenBank Accession L05628; GI: 292332; March 29, 1993).

Zamane et al. do not teach a method for detection of a molecule having SEQ ID NO: 171 which comprises contacting a solid support with a polynucleotide having SEQ ID NO: 171 and

determining binding of said polynucleotide in said sample to immobilized targets. Cole et al. teach analysis of gene expression of MRP-1 by northern blot in which cDNA fragments of MRP-1 are bound to a membrane and sample molecules are contacted to the support, and binding of the polynucleotide in the sample to said immobilized polynucleotides is determined (Figure 1A).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the polynucleotides taught by Zaman et al. using the methods taught by Cole et al. One would have been motivated to undertake such experimentation in order to have provided more information about the expression of MRP-1 in sample nucleic acids for further understanding of the multidrug resistance phenomena.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be

viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

March 5, 2007